29 March 2001

Set	Items	Description
S1	602	CANDIDA (S)(LANOSTEROL OR ERG OR DESATURASE)
S2	54	S1 AND (AZOLE (2N) RESISTANT)
S3	16	RD (unique items)
S4	14	S3 NOT PY>1998
S5	10	S3 NOT PY>=1998
S6	4	S5 AND ALBICAN?

6/5/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11331263 BIOSIS NO.: 199800112595
Resistance to azoles in %Candida% %albicans% caused by mutations in the %lanosterol% 14a-demethylase gene.
AUTHOR: Ryder N S(a); Favre B
AUTHOR ADDRESS: (a)Novartis Res. Inst., Brunner-Strasse 59, Vienna A-1235** Austria
JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 37p48 1997
CONFERENCE/MEETING: 37th Interscience Conference on Antimicrobial Agents and Chemotherapy Toronto, Ontario, Canada September 28-October 1, 1997
SPONSOR: ICAAC
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 109-97-7D: AZOLES; 109-97-7: AZOLE; 86386-73-4: FLUCONAZOLE; 91161-71-6: TERBINAFINE; 9029-62-3: SQUALENE EPOXIDASE; 65277-42-1: KETOCONAZOLE
DESCRIPTORS:
MAJOR CONCEPTS: Genetics; Pharmacology
BIOSYSTEMATIC NAMES: Ascomycetes--Fungi, Plantae; Fungi Imperfecti or Deuteromycetes--Fungi, Plantae
ORGANISMS: Candida-%albicans% (Fungi Imperfecti or Deuteromycetes)--%azole%-%resistant% isolate; Saccharomyces-cerevisiae (Ascomycetes
BIOSYSTEMATIC CLASSIFICATION (SUPER TAXA): Fungi; Microorganisms; Nonvascular Plants; Plants
CHEMICALS & BIOCHEMICALS: fluconazole--antifungal-drug; ketoconazole--antifungal-drug; lanosterol 14a-demethylase gene--mutation; terbinafine--squalene epoxidase inhibitor
MISCELLANEOUS TERMS: amino acid sequence; Meeting Abstract; Meeting Poster
CONCEPT CODES:
03502 Genetics and Cytogenetics-General
10060 Biochemical Studies-General
10802 Enzymes-General and Comparative Studies; Coenzymes
36001 Medical and Clinical Microbiology-General; Methods and Techniques
38502 Chemotherapy-General; Methods; Metabolism
00520 General Biology-Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals
BIOSYSTEMATIC CODES:
15100 Ascomycetes
15500 Fungi Imperfecti or Deuteromycetes

6/5/2 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02107022 Genuine Article#: KA934 Number of References: 42
Title: CHARACTERIZATION OF AN %AZOLE%-%RESISTANT% CANDIDA-GLABRATA ISOLATE
Author(s): VANDENBOSSCHE H; MARICHAL P; ODDS FC; LEJEUNE L; COENE MC
Corporate Source: JANSSEN RES FDN,DIV MED & CHEM & PHARMACOL/B-2340 BEERSE//BELGIUM/
Journal: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, 1992, V36, N12 (DEC), P 2602-2610
ISSN: 0066-4804
Language: ENGLISH Document Type: ARTICLE

...Current Contents, Life Sciences
Journal Subject Category: PHARMACOLOGY & PHARMACY; MICROBIOLOGY
Abstract: A %Candida% (Torulopsis) glabrata strain (B57149) became resistant to fluconazole after a patient carrying the organism was treated with the drug at 400 mg once daily for 9 days. Growth of the pretreatment isolate (B57148) was inhibited by 50% with 0.67 muM ketoconazole, 1.0 muM itraconazole, and 43 muM fluconazole, whereas growth of B57149 was inhibited slightly by 10 muM ketoconazole but was unaffected by 10 muM itraconazole or 100 muM fluconazole. This indicates cross-resistance to all three azole antifungal agents. The cellular fluconazole content of B57149 was from 1.5- to 3-fold lower than that of B57148, suggesting a difference in drug uptake between the strains. However, this difference was smaller than the measured difference in susceptibility and, therefore, cannot fully explain the fluconazole resistance of B57149. Moreover, the intracellular contents of ketoconazole and itraconazole differed by less than twofold between the strains, so that uptake differences did not account for the azole cross-resistance of B57149. The microsomal cytochrome P-450 content of B57149 was about twice that of B57148, a difference quantitatively similar to the increased subcellular ergosterol synthesis from mevalonate or %lanosterol%. These results indicate that the level of P-450-dependent 14alpha-demethylation of %lanosterol% is higher in B57149. Increased ergosterol synthesis was also seen in intact B57149 cells, and this coincided with a decreased susceptibility of B57149 toward all three azoles and amphotericin B. B57149 also had higher squalene epoxidase activity, and thus, more terbinafine was needed to inhibit the synthesis of 2,3-oxidosqualene from squalene. P-450 content and ergosterol synthesis both decreased when isolate B57149 was subcultured repeatedly on drug-free medium. This repeated subculture also fully restored the strain's itraconazole susceptibility, but only partly increased its susceptibility to fluconazole. The results suggest that both lower fluconazole uptake and increased P-450-dependent ergosterol synthesis are involved in the mechanism of fluconazole resistance but that only the increased ergosterol synthesis contributes to itraconazole cross-resistance.
Identifiers--KeyWords Plus: SACCHAROMYCES-CEREVISIAE; %ALBICANS% RESISTANCE; GENE; CYTOCHROME-P-450; MICONAZOLE; STRAIN; 14-ALPHA-DEMETHYLASE; SUSCEPTIBILITY; FLUOCONAZOLE; ITRACONAZOLE
Research Fronts: 90-5891 001 (STEROL BIOSYNTHESIS INHIBITORS; INVITRO AMPLIFICATION; CANDIDA-%ALBICANS% DARLINGTON STRAIN)
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6/5/3 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09184370 97354377

The presence of an R467K amino acid substitution and loss of allelic variation correlate with an %azole%-%resistant% %lanosterol% 14alpha demethylase in %Candida% %albicans%.

White TC
Department of Pathobiology, School of Public Health and Community Medicine, University of Washington, and Seattle Biomedical Research Institute, 98109, USA. tedwhite@u.washington.edu

Antimicrob Agents Chemother (UNITED STATES) Jul 1997, 41 (7) p1488-94, ISSN 0066-4804 Journal Code: 6HK
Contract/Grant No.: RO1 DE-11367, DE, NIDR
Languages: ENGLISH
Document type: JOURNAL ARTICLE
JOURNAL ANNOUNCEMENT: 9711
Subfile: INDEX MEDICUS

Azole resistance in the pathogenic yeast %Candida% %albicans% is an emerging problem in the human immunodeficiency virus (HIV)-infected population. The target enzyme of the azole drugs is %lanosterol% 14alpha demethylase (Erg16p), a cytochrome P-450 enzyme in the biosynthetic pathway of ergosterol. Biochemical analysis demonstrates that Erg16p became less susceptible to fluconazole in isolate 13 in a series of isolates from an HIV-infected patient. PCR-single-strand conformation polymorphism (PCR-SSCP) analysis was used to scan for genomic alterations of ERG16 in the isolates that would cause this change in the enzyme in isolate 13. Alterations near the 3' end of the gene that were identified by PCR-SSCP were confirmed by DNA sequencing. A single amino acid substitution (R467K) that occurred in isolate 13 was identified in both alleles of ERG16. Allelic differences within the ERG16 gene, in the ERG16 promoter, and in the downstream THR1 gene were eliminated in isolate 13. The loss of allelic variation in this region of the genome is most likely the result of mitotic recombination or gene conversion. The R467K mutation and loss of allelic variation that occur in isolate 13 are likely responsible for the %azole%-%resistant% enzyme activity seen in this and subsequent isolates. The description of R467K represents the first point mutation to be identified within ERG16 of a clinical isolate of C. %albicans% that alters the fluconazole sensitivity of the enzyme.

Tags: Human; Support, U.S. Gov't, P.H.S.
Descriptors: Antifungal Agents--Pharmacology--PD; *Candida %albicans% --Drug Effects--DE; *Cytochrome P-450--Drug Effects--DE; *Fluconazole --Pharmacology--PD; *Oxidoreductases--Drug Effects--DE; *Variation (Genetics); Alleles; Base Sequence; Candida %albicans%--Enzymology--EN; Cloning, Molecular; Drug Resistance, Microbial; Molecular Sequence Data;

...Regions (Genetics); Sequence Analysis
Molecular Sequence Databank No.: GENBANK/U67192; GENBANK/U67193
CAS Registry No.: 0 (Antifungal Agents); 86386-73-4 (Fluconazole); 9035-51-2 (Cytochrome P-450)
Enzyme No.: EC 1. (Oxidoreductases); EC 1.- (lanosterol 14 alpha-demethylase)

6/5/4 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05272557 87197973
The lipid composition and permeability to azole of an %azole%- and polyene-%resistant% mutant of Candida %albicans%.
Hitchcock CA; Barrett-Bee KJ; Russell NJ
J Med Vet Mycol (ENGLAND) Feb 1987, 25 (1) p29-37, ISSN 0268-1218
Journal Code: JMD
Languages: ENGLISH
Document type: JOURNAL ARTICLE
JOURNAL ANNOUNCEMENT: 8708
Subfile: INDEX MEDICUS
%Candida% %albicans% 6.4, which is resistant to both polyene and azole groups of antifungal antibiotics, has a larger lipid content and lower polar lipid to neutral lipid ratio compared with other strains that are sensitive or resistant only to azoles. C. %albicans% 6.4 contains a relatively greater proportion of triacylglycerol in its neutral lipid in the exponential phase of batch culture compared with other strains, but, unlike them, does not accumulate triacylglycerols or any other stored lipid in the stationary phase. Like other strains, in C. %albicans% 6.4 the major phospholipids are phosphatidylcholine, phosphatidylethanolamine and phosphatidylinositol, but sphingomyelin is absent; the major fatty acids are palmitic, palmitoleic, oleic and linoleic acids. In common with other C. %albicans% strains, strain 6.4 contains non-specific (lyso)phospholipase activity. The main distinctive feature of the lipid composition of C. %albicans% 6.4 is the absence of ergosterol, which is replaced by methylated sterol; mainly %lanosterol%, 24-methylene-24,25-dihydrolanostero 1 and 4-methylergostadiene-3-ol. It is suggested that the altered membrane sterol pattern provides a common basis for the double resistance by preventing polyene binding and reducing azole permeability.
Descriptors: Antibiotics, Antifungal--Pharmacology--PD; *Antifungal Agents--Pharmacology--PD; *Candida %albicans%--Drug Effects--DE; *Lipids --Analysis--AN; *Triazoles--Pharmacology--PD; Antifungal Agents--Metabolism --ME; Azoles--Pharmacology--PD; Candida %albicans%--Analysis--AN; Candida %albicans%--Genetics--GE; Candida %albicans%--Metabolism--ME; Drug Resistance, Microbial; Mutation; Permeability; Polyenes--Pharmacology--PD; Triazoles--Metabolism--ME
CAS Registry No.: 0 (Antibiotics, Antifungal); 0 (Antifungal Agents); 0 (Azoles); 0 (Polyenes); 0 (Triazoles); 76674-22-1 (ICI 153066)

	L #	Hits	Search Text	DBs	Time Stamp
1	L2	7	candida same (azole near3 resist$)	USPAT	2000/03/29 08:58
2	L4	2	(lanosterol adj demethylase) near9 candida	USPAT	2000/03/29 09:01
3	L5	10	(Lanosterol adj demethylase)or erg16 or (sterol adj desaturase)	USPAT	2000/03/29 09:03
4	L7	6	5 and candida	USPAT	2000/03/29 09:03

?s s2 and (azole (n4) re[redacted]t?)
55 S2
6351 AZOLE
2095732 RESIST?
1159 AZOLE(4N)RESIST?
S3 4 S2 AND (AZOLE (N4) RESIST?)
?t s3/5/all

3/5/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09446461 98139008
Amino acid substitutions in the cytochrome P-450 lanosterol **14alpha-** demethylase **(CYP51A1) from** azole- resistant **Candida albicans clinical isolates contribute to** resistance **to** azole **antifungal agents.**
Sanglard D; Ischer F; Koymans L; Bille J
Institut de Microbiologie, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. dsanglar@eliot.unil.ch
Antimicrob Agents Chemother (UNITED STATES) Feb 1998, 42 (2) p241-53, ISSN 0066-4804 Journal Code: 6HK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
JOURNAL ANNOUNCEMENT: 9806
Subfile: INDEX MEDICUS
The cytochrome P-450 **lanosterol** 14alpha- **demethylase** (CYP51A1) of yeasts is involved in an important step in the biosynthesis of ergosterol. Since CYP51A1 is the target of azole antifungal agents, this enzyme is potentially prone to alterations leading to resistance to these agents. Among them, a decrease in the affinity of CYP51A1 for these agents is possible. We showed in a group of Candida albicans isolates from AIDS patients that multidrug efflux transporters were playing an important role in the **resistance** of C. albicans to **azole** antifungal agents, but without excluding the involvement of other factors (D. Sanglard, K. Kuchler, F. Ischer, J.-L. Pagani, M. Monod, and J. Bille, Antimicrob. Agents Chemother. 39:2378-2386, 1995). We therefore analyzed in closer detail changes in the affinity of CYP51A1 for azole antifungal agents. A strategy consisting of functional expression in Saccharomyces cerevisiae of the C. albicans CYP51A1 genes of sequential clinical isolates from patients was designed. This selection, which was coupled with a test of susceptibility to the azole derivatives fluconazole, ketoconazole, and itraconazole, enabled the **detection** of mutations in different cloned CYP51A1 genes, whose products are potentially affected in their affinity for azole derivatives. This selection enabled the **detection** of five different mutations in the cloned CYP51A1 genes which correlated with the occurrence of **azole resistance** in clinical C. albicans isolates. These mutations were as follows: replacement of the glycine at position 129 with alanine (G129A), Y132H, S405F, G464S, and R467K. While the S405F mutation was found as a single amino acid substitution in a CYP51A1 gene from an **azole - resistant** yeast, other mutations were found simultaneously in individual CYP51A1 genes, i.e., R467K with G464S, S405F with Y132H, G129A with G464S, and R467K with G464S and Y132H. Site-directed mutagenesis of a wild-type CYP51A1 gene was performed to estimate the effect of each of these mutations on **resistance** to **azole** derivatives. Each single mutation, with the exception of G129A, had a measurable effect on the affinity of the target enzyme for specific azole derivatives. We speculate that these specific mutations could combine with the effect of multidrug efflux transporters in the clinical isolates and contribute to different patterns and stepwise increases in **resistance** to **azole** derivatives.
Tags: Human; Support, Non-U.S. Gov't
Descriptors: *Antifungal Agents--Pharmacology--PD; *Candida albicans --Drug Effects--DE; *Candida albicans--Enzymology--EN; *Cytochrome P-450 --Genetics--GE; *Fluconazole--Pharmacology--PD; *Fungal Proteins--Genetics --GE; *Oxidoreductases--Genetics--GE; Amino Acid Sequence; Azoles --Pharmacology--PD; Cytochrome P-450--Chemistry--CH; Drug Resistance, Microbial--Genetics--GE; Fungal Proteins--Chemistry--CH; Microbial Sensitivity Tests; Molecular Sequence Data; Mutagenesis, Site-Directed; Oxidoreductases--Chemistry--CH; Protein Structure, Secondary

CAS Registry No.: 0 (Antifungal Agents); 0 (Azoles); 0 (Fungal Proteins); 86386-73-4 (Fluconazole); 9035-51-2 (Cytochrome P-450)
Enzyme No.: EC 1. (Oxidoreductases); EC 1.- (**lanosterol** 14 alpha-**demethylase**)

09/284,155

3/5/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09309727 97472183
Molecular biological characterization of an azole- resistant **Candida glabrata isolate.**
Marichal P; Vanden Bossche H; Odds FC; Nobels G; Warnock DW; Timmerman V; Van Broeckhoven C; Fay S; Mose-Larsen P
Anti-Infectives Research Departments, Janssen Research Foundation, Beerse, Belgium. pmaricha@janbe.jnj.com
Antimicrob Agents Chemother (UNITED STATES) Oct 1997, 41 (10) p2229-37, ISSN 0066-4804 Journal Code: 6HK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
JOURNAL ANNOUNCEMENT: 9801
Subfile: INDEX MEDICUS
Two isolates of Candida glabrata, one susceptible and one **resistant** to **azole** antifungals, were previously shown to differ in quantity and activity of the cytochrome P-450 14alpha-**lanosterol demethylase** which is the target for **azole** antifungals. The **resistant** isolate also had a lower intracellular level of fluconazole, but not of ketoconazole or itraconazole, than the susceptible isolate. In the present study a 3.7-fold increase in the copy number of the CYP51 gene, encoding the 14alpha-**lanosterol demethylase** , was found. The amount of CYP51 mRNA transcript in the resistant isolate was eight times greater than it was in the susceptible isolate. **Hybridization** experiments on chromosomal blots indicated that this increase in copy number was due to duplication of the entire chromosome containing the CYP51 gene. The phenotypic instability of the resistant isolate was demonstrated genotypically: a gradual loss of the duplicated chromosome was seen in successive subcultures of the isolate in fluconazole-free medium and correlated with reversion to susceptibility. The greater abundance of the amplified chromosome induced pronounced differences in the protein patterns of the susceptible and revertant isolates versus that of the resistant isolate, as demonstrated by two-dimensional gel electrophoresis (2D-GE). Densitometry of the 2D-GE product indicated upregulation of at least 25 proteins and downregulation of at least 76 proteins in the resistant isolate.
Tags: Case Report; Female; Human; Support, Non-U.S. Gov't
Descriptors: *Antifungal Agents--Pharmacology--PD; *Azoles--Pharmacology--PD; *Candida--Drug Effects--DE; *Candidiasis, Vulvovaginal--Microbiology--MI; Antifungal Agents--Metabolism--ME; Azoles--Metabolism--ME; Base Sequence; Candida--Genetics--GE; Candida--Metabolism--ME; Culture Media; Drug Resistance, Microbial--Genetics--GE; DNA Probes; DNA, Fungal--Biosynthesis--BI; DNA, Fungal--Isolation and Purification--IP; Fungal Proteins--Biosynthesis--BI; Fungal Proteins--Genetics--GE; Gene Expression Regulation, Enzymologic--Drug Effects--DE; Gene Expression Regulation, Fungal--Drug Effects--DE; Genes, Fungal--Genetics--GE; Middle Age; Molecular Sequence Data; Mutation--Genetics--GE; Mutation--Physiology--PH; RNA, Fungal--Biosynthesis--BI; RNA, Fungal--Isolation and Purification--IP
Molecular Sequence Databank No.: GENBANK/AF006033
CAS Registry No.: 0 (Antifungal Agents); 0 (Azoles); 0 (Culture Media); 0 (DNA Probes); 0 (DNA, Fungal); 0 (Fungal Proteins); 0 (RNA, Fungal)

3/5/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08541933 96161286
Deletion of the Candida glabrata ERG3 and ERG11 genes: effect on cell

viability, cell growth, [redacted]rol composition, and antifungal [redacted]usceptibility.
Geber A; Hitchcock CA; Swartz JE; Pullen FS; Marsden KE; Kwon-Chung KJ; Bennett JE
Department of Medicine, George Washington University Medical Center, Washington, D.C. 20037, USA.
Antimicrob Agents Chemother (UNITED STATES) Dec 1995, 39 (12) p2708-17 , ISSN 0066-4804 Journal Code: 6HK
Languages: ENGLISH
Document type: JOURNAL ARTICLE
JOURNAL ANNOUNCEMENT: 9606
Subfile: INDEX MEDICUS
We have cloned and sequenced the structural genes encoding the delta 5,6 sterol desaturase (ERG3 gene) and the 14 alpha-methyl sterol **demethylase** (ERG11 gene) from Candida glabrata L5 (leu2). Single and double mutants of these genes were created by gene deletion. The phenotypes of these mutants, including sterol profiles, aerobic viabilities, antifungal susceptibilities, and generation times, were studied. Strain L5D (erg3 delta::LEU2) accumulated mainly ergosta-7,22-dien-3 beta-ol, was aerobically viable, and remained susceptible to antifungal agents but had a slower generation time than its parent strain. L5LUD (LEU2 erg11 delta::URA3) strains required medium supplemented with ergosterol and an anaerobic environment for growth. A spontaneous aerobically viable mutant, L5LUD40R (LEU erg11 delta::URA3), obtained from L5LUD (LEU2 erg11 delta::URA3), was found to accumulate **lanosterol** and obtusifoliol, was **resistant** to **azole** antifungal agents, demonstrated some increase in resistance to amphotericin B, and exhibited a 1.86-fold increase in generation time in comparison with L5 (leu2). The double-deletion mutant L5DUD61 (erg3 delta::LEU2 erg11 delta::URA3) was aerobically viable, produced mainly 14 alpha-methyl fecosterol, and had the same antifungal susceptibility pattern as L5LUD40R (LEU2 erg11 delta::URA3), and its generation time was threefold greater than that of L5 (leu2). Northern (RNA) analysis revealed that the single-deletion mutants had a marked increase in message for the undeleted ERG3 and ERG11 genes. These results indicate that differences in antifungal susceptibilities and the restoration of aerobic viability exist between the C. glabrata ergosterol mutants created in this study and those sterol mutants with similar genetic lesions previously reported for Saccharomyces cerevisiae.
Tags: Support, Non-U.S. Gov't
Descriptors: *Antifungal Agents--Pharmacology--PD; *Candida--Genetics--GE ; *Cytochrome P-450--Genetics--GE; *Genes, Structural, Fungal--Genetics--GE ; *Oxidoreductases--Genetics--GE; *Sterols--Metabolism--ME; Base Sequence; Blotting, Northern; Candida--Drug Effects--DE; Candida--Enzymology--EN; Cloning, Molecular; DNA, Fungal--Biosynthesis--BI; DNA, Fungal--Genetics --GE; Gene Deletion; Leucine--Metabolism--ME; Molecular Sequence Data; Nucleic Acid **Hybridization** ; Transformation, Genetic
Molecular Sequence Databank No.: GENBANK/L40389; GENBANK/L40390
CAS Registry No.: 0 (Antifungal Agents); 0 (DNA, Fungal); 0 (Sterols); 7005-03-0 (Leucine); 9035-51-2 (Cytochrome P-450)
Enzyme No.: EC 1. (Oxidoreductases); EC 1.- (**lanosterol** 14 alpha-**demethylase**); EC 1.3.- (sterol delta-5 desaturase)

3/5/4 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07288240 Genuine Article#: 146MX Number of References: 34
Title: The antifungal activity of 2,2'-diamino-4,4'-dithiazole derivatives is due to the possible inhibition of lanosterol-**14-alpha-** demethylase

Author(s): Scozzafava A; Nicolae A; Maior O; Briganti F; Supuran CT (REPRINT)
Corporate Source: UNIV FLORENCE,LAB CHIM INORGAN & BIOINORGAN, VIA GINO CAPPONI 7/I-50121 FLORENCE//ITALY/ (REPRINT); UNIV FLORENCE,LAB CHIM INORGAN & BIOINORGAN/I-50121 FLORENCE//ITALY/; UNIV BUCHAREST,DEPT CHIM ORGAN/BUCHAREST//ROMANIA/
Journal: JOURNAL OF ENZYME INHIBITION, 1998, V14, N1, P49-68
ISSN: 8755-5093 Publication date: 19980000

Publisher: HARWOOD ACAD [redacted] L GMBH, C/O STBS LTD, PO BOX 9[redacted] READING RG1 8JL, BERKS, ENGLAND
Language: English Document Type: ARTICLE
Geographic Location: ITALY; ROMANIA
Subfile: CC LIFE--Current Contents, Life Sciences
Journal Subject Category: BIOCHEMISTRY & MOLECULAR BIOLOGY
Abstract: Aryl/alkyl sulfonylamido-, arylsulfenylamido-, arylcarboxamido- and ureido/thioureido/guanidine derivatives of 2,2'-diamino-4,4'-dithiazole were prepared by reaction of the title compound with sulfonyl/sulfenyl halides, sulfonic acid anhydrides, acyl chlorides, tosyl isocyanate, aryl/allyl isocyanates or isothiocyanates. Mono- as well as bis-derivatized compounds have been obtained. Several of the newly synthesized compounds act as effective antifungal agents against Aspergillus and Candida spp., some of them showed activities comparable to ketoconazole (with minimum inhibitory concentrations in the range of 0.2-1.8 mu g/mL) but possessed lower activity as compared to itraconazole. Greatest activity was **detected** against A. niger, and least activity against C. albicans. The mechanism of action of these compounds probably involves inhibition of ergosterol biosynthesis, and interaction with **lanosterol** -14-alpha-**demethylase** (CYP51A1), since reduced amounts of ergosterol were found by means of HPLC in cultures of the sensitive strain A. niger treated with some of these inhibitors. Thus, the compounds reported here and the azole antifungal derivatives might possess a similar mechanism of action at molecular level.
Descriptors--Author Keywords: 2,2'-diamino-4,4'-dithiazole ; sulfonamides ; (thio)ureas ; antifungal compounds ; **lanosterol** -14-alpha-**demethylase** ; ergosterol biosynthesis inhibitors
Identifiers--KeyWord Plus(R): IN-VITRO SUSCEPTIBILITY; **AZOLE** ANTIFUNGALS; CANDIDA-ALBICANS; **LANOSTEROL**; **RESISTANCE**; ITRACONAZOLE; 14-ALPHA-**DEMETHYLASE** ; CYTOCHROME-P-450; **DEMETHYLASE**; MECHANISMS
Cited References:
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BARBOIU M, 1996, V3, P233, METAL BASED DRUGS
BEYER H, 1951, V84, P518, CHEM BER
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Set Items Description

S1	158	(DEMETHYL[redacted]E(S)LANOSTEROL)AND (DETECT? OR [redacted]BRIDIZ?)
S2	55	RD (unique items)
S3	4	S2 AND (AZOLE (N4) RESIST?)